(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 June 2001 (28.06.2001)

PCT

(10) International Publication Number
WO 01/45694 A1

(51) International Patent Classification[7]: A61K 31/18, 31/38, 31/335, 31/44, 31/425, C07C 303/38, 311/21, 311/29, 311/44, C07D 213/89, 271/12, 285/14, 333/34, 333/52, 333/72

(21) International Application Number: PCT/US00/34574

(22) International Filing Date:
19 December 2000 (19.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/172,807 21 December 1999 (21.12.1999) US

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(81) Designated States *(national)*: AE, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/45694 A1

(54) Title: UROTENSIN-II RECEPTOR ANTAGONISTS

(57) Abstract: The present invention relates to sulfonamides, pharmaceutical compositions containing them, and their use as antagonists of urotensin II.

UROTENSIN-II RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to sulfonamides, pharmaceutical compositions containing them and their use as urotensin II antagonists

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation. Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction

  both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract, respiratory, and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide

- osmoregulation:

  effects which include the modulation of transepithelial ion (Na^+, Cl^-) transport. Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)

- metabolism:

  urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish (activating triacylglycerol lipase resulting in the mobilization of non-esterified free fatty acids)

  (Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* **1980**, *77*, 5021; Conlon, *et. al. J. Exp. Zool.* **1996**, *275*, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* **1999**, *401*, 282)

Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, restenosis, asthma, (Hay DWP, Luttmann MA, Douglas SA: 2000, Br J Pharmacol: volume 131, pages 10-12) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* **1999**, *401*, 282), they also may be useful in the treatment of addiction, schizophrenia, impulsivity, anxiety, stress, depression, and neuromuscular function. Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* **1999**, *401*, 282, Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999)

SUMMARY OF THE INVENTION

In one aspect this invention provides for sulfonamides and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of sulfonamides as antagonists of urotensin II, and as inhibitors of urotensin II.

In another aspect, this invention provides for the use of sulfonamides for treating conditions associated with urotensin II imbalance.

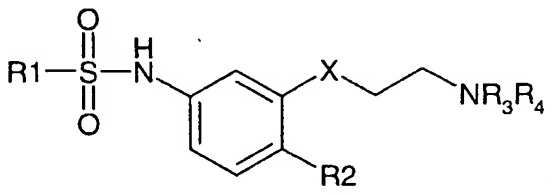
In yet another aspect, this invention provides for the use of sulfonamides for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, restenosis, asthma, neurogenic inflammation and metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function, and diabetes.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula(I):



Formula (I)

wherein:

R_1 is phenyl, benzothiophenyl, thienyl, furyl, pyrrolyl, pyridinyl, benzthiadiazoyl, benzoxadiazoyl, quinolinyl, or naphthyl, all of which may be substituted or unsubstituted by one, two, three, four or five of the following: halogen, methoxy, OH, NO_2, YCF_3, C_{1-4} alkyl, $C_{(0-4)}alkylCO_2C_{(0-4)}alkyl$, cyano, $cycloC_{(1-4)}alkylenedioxy$, or dimethylamino;

R_2 is halogen, CN or methyl;

R_3 and R_4 are independently hydrogen, C_{1-6} alkyl or benzyl; or with the nitrogen form a pyrrolidine or piperidine ring;

X is O or CH_2;

Y is a bond or O;

provided the compound of Formula (I) is not 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [3-(2-dimethylamino-ethoxy)-4-iodo-phenyl]-amide;

or a pharmaceutically acceptable salt thereof.

When used herein, the term "alkyl" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

Preferably R_1 is phenyl, thienyl, pyridinyl, benzthiadiazoyl, benzoxadiazoyl, or naphthyl, all of which may be substituted or unsubstituted by one, two, or three of the following: halogen, methoxy, NO_2, YCF_3, or C_{1-4} alkyl.

Preferably R_2 is halogen.

Preferably R_3 is alkyl; more preferably R_3 is methyl or ethyl.

Preferably R_4 is alkyl; more preferably R_4 is methyl or ethyl.

Preferably X is O.

Preferably Y is a bond.

Preferred Compounds are:

N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;
4-Bromo-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
N-[4-Methyl-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;
N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3-methoxy-benzenesulfonamide;
N-[4-Bromo-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;
N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;
4,5-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
3,4-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,4,6-Trichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,6-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide;
2-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide;
4-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
4-Iodo-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,3-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Chloro-4-fluoro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Chloro-4-methyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,5-Dimethyl-4-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Chloro-4-trifluoromethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,4-Dichloro-6-methyl-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Methoxy-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,5-Dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,5-Dimethoxy-N-[4-bromo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Nitro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Nitro-4-methoxy-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Nitro-4-methyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Ethyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3,4-Dichlorophenyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,4,6-Trimethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
4-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-naphthalenesulfonamide;
5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
2,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3-thiophenesulfonamide;
5-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
4,5-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}methyl)-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzo[1,2,5]-4-thiadiazolesulfonamide;
2,4-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Methyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,6-Dimethyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Methoxy-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,4-Dichloro-5-methyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3-Nitro-4-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Nitro-4-trifluoromethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-1-naphthalenesulfonamide;
4-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
3-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
4-Nitro-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
4,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
7-Chloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzo[1,2,5]oxadiazole-4-sulfonamide;
5-Bromo-6-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3-pyridinesulfonamide;
2,4-Dibromo-5-methoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Methyl-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,6-Dimethyl-4-bromo-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3,4-Dimethoxy-N-[4-chloro-3-(2-methylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Bromo-4,5-dimethoxy-N-[4-chloro-3-(2-methylamino-ethoxy)-phenyl]-benzenesulfonamide;
5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-naphthalenesulfonamide;
2,6-Dichloro-4-trifluoromethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;
4,5-Dibromo-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
2-Bromo-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3,4-Dimethoxy-N-[4-chloro-3-(3-dimethylamino-propyl)-phenyl]-benzenesulfonamide;
3,4-Dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide; and

2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide.

More preferred compounds are:

N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;
4,5-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
3,4-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,4,6-Trichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,6-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide;
N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;
2-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide;
2,4-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Methyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,6-Dimethyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Methoxy-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,4-Dichloro-5-methyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Nitro-4-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Nitro-4-trifluoromethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
4-Chlorophenyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-1-naphthalenesulfonamide;
4-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
3-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
4-Nitro-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
4,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
7-Chloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzo[1,2,5]oxadiazole-4-sulfonamide;

5-Bromo-6-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3-pyridinesulfonamide;

2,4-Dibromo-5-methoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2-Methyl-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,6-Dichloro-4-trifluoromethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;

4,5-Dibromo-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;

2-Bromo-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3,4-Dimethoxy-N-[4-chloro-3-(3-dimethylamino-propyl)-phenyl]-benzenesulfonamide;

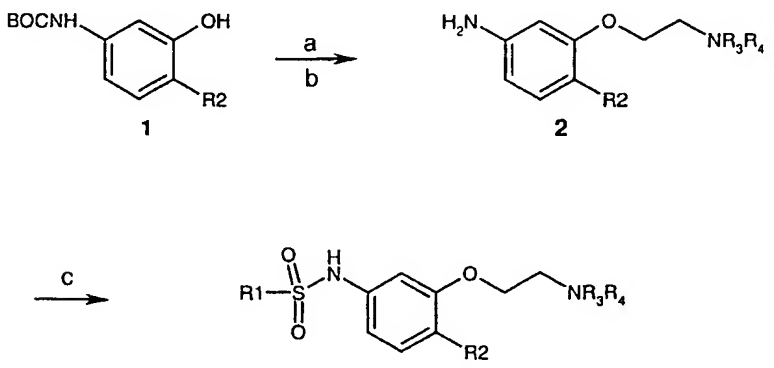
3,4-Dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide; and

2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide.

Compounds of Formula (I) were prepared as outlined in Scheme 1.

Scheme 1



1 2 3

Conditions: a) $ClCH_2CH_2NR_3R_4$-hydrochloride, potassium carbonate, water/1,2-dimethoxyethane, reflux; b) HCl; c) R_1SO_2Cl, $CHCl_3$, ambient temperature. (R_1, R_3 and R_4 as defined above)

For example, phenol **1** was alkylated with various dialkylaminoethyl chlorides and the resulting ethers deprotected to provide the anilines **2**. Subsequent sulfonylation of the anilines furnished the target compounds **3**.

With appropriate manipulation, including the use of alternative nitrogen protecting group(s), the synthesis of the remaining compounds of Formula (I) was accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

These sulphonamide analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, restenosis, asthma, neurogenic inflammation and metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function, and diabetes.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [125I] h-U-II (200 Ci/mmol^{-1} in the presence of increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl2). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. ^{125}I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was defined by ^{125}I U-II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.

Ca^{2+}-mobilization:

A microtitre plate based Ca^{2+}-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC50)was calculated for various test compounds.

Inositol phosphates assays:

HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[^{3}H] inositol per ml of inositol free Dulbecco's modified Eagel's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1μM) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in

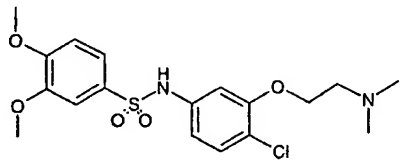
formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate was eluted with 4ml of 1M ammonium formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter. Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): Ki = 50 nM – 10000 nM (example 8 Ki = 1300 nM)

The following Examples are illustrative but not limiting embodiments of the present invention.

Example 1

N-[4-Chloro-3-(2-dimethylamino-ethoxy)phenyl]-3,4-dimethoxy-benzenesulfonamide



a). 2-Chloro-5-aminophenol

2-Chloro-5-nitroanisole (310 g, 1.7 mol) was taken up in a mixture of 48% HBr (1.5 L) and AcOH (1.2 L) and heated at reflux for 3 days. The dark solution was allowed to cool to room temperature, poured into ice water (10 L), and let stand for 3 h. The resultant dull yellow solid was filtered, washed with water, and dried in vacuo (230 g, 79%): mp 115-117°C.

b). 2-Chloro-5-aminophenol

A solution of 2-chloro-5-nitrophenol (25 g, 0.14 mol) in ethyl acetate (150 mL) was treated with 5% Pt/C (250mg) and the mixture shaken under a hydrogen atmosphere (30 psi) for 4h. The mixture was filtered through Celite® and the residue washed well with hot ethyl acetate. The filtrate was treated with activated charcoal and re-filtered as above. Evaporation of the ethyl acetate gave a solid (19.8 g, 98%).

c). 4-Chloro-3-hydroxyphenylcarbamic acid tert-butyl ester

To a solution of 2-chloro-5-aminophenol (20 g, 0.14 mol) in THF (150 mL) was added a solution of di-*tert*-butyl dicarbonate (33 g, 0.15 mol) in THF (150 mL). The reaction was heated at reflux for 6 h, at which time it was allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue diluted with ether (500 mL) and washed with 1 M citric acid (2 x 300 mL). The aqueous washings were extracted with ether (300 mL) and the combined organics washed with brine (300 mL), dried ($MgSO_4$), and concentrated.

The resultant brown solid was triturated with hexanes and dried in vacuo to give 33 g (97%) of the title compound: mp 103-106 °C.

d). 3-[2-(N,N-Dimethylamino)ethoxy]-4-chloroaniline

To a solution of 4-chloro-3-hydroxyphenylcarbamic acid *tert*-butyl ester (140 mg, 0.57 mmol) in 4:1 DME/water (5 mL) was added dimethylaminoethyl chloride hydrochloride (90 mg, 0.63 mmol) and K_2CO_3 (320 mg, 2.3 mmol). The reaction mixture was heated at reflux for 16 h, at which time it was allowed to cool to room temperature. The DME was removed *in vacuo* and the residue treated with 6 N HCl (2 mL). The resultant mixture was stirred at room temperature for 2 h, at which time it was diluted with water (5 mL) and washed with EtOAc (5 mL). The aqueous layer was basified with solid K_2CO_3 and extracted with EtOAc (2 x 10 mL). The EtOAc layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give 60 mg (50%) of the title compound.

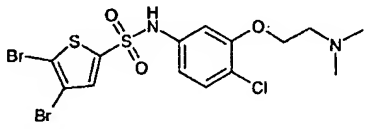
e). N-[4-Chloro-3-(2-dimethylamino-ethoxy)phenyl]-3,4-dimethoxy-benzenesulfonamide

3-[2-(N,N-Dimethylamino)ethoxy]-4-chloroaniline (1.00g, 4.66 mmol) was dissolved in 15 mL $CHCl_3$. A solution of 3,4-dimethoxybenzenesulfonyl chloride (1.10g, 4.66 mmol) in 14 mL $CHCl_3$ was added and the solution was allowed to stir overnight. Diethyl ether was added to the cloudy white mixture and the white product (1.97g, 94%) was filtered and dried. Recrystallisation from hot methanol gave sparkling white crystals which were filtered and dried: mp 228-229°C; MS (ES+) m/e 415 $[M+H]^+$

The compounds of Examples 2 - 6 were prepared by using the general procedure(s) of Example 1 above with appropriate substitution of reactants:

Example 2

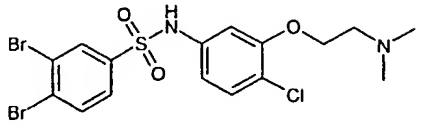
4,5-Dibromo-thiophene-2-sulfonic acid [4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-amide.



Prepared from 4,5-dibromo-thiophene-2-sulfonyl chloride and 3-[2-(N,N-dimethylamino)ethoxy]-4-chloroaniline. MS (ES+) m/e 517 $[M+H]^+$.

Example 3

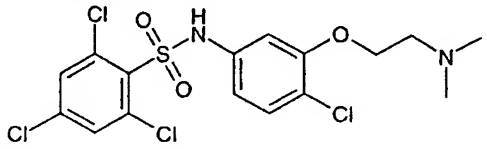
3,4-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide.



Prepared from 3,4-dibromobenzenesulfonyl chloride and 3-[2-(N,N-dimethylamino)ethoxy]-4-chloroaniline. MS (ES+) m/e 511 $[M+H]^+$.

Example 4

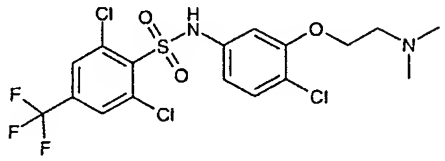
2,4,6-Trichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide.



Prepared from 2,4,6-trichlorobenzenesulfonyl chloride and 3-[2-(N,N-dimethylamino)ethoxy]-4-chloroaniline. MS (ES+) m/e 457 $[M+H]^+$

Example 5

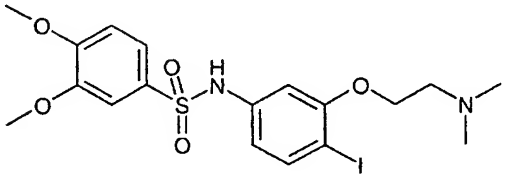
2,6-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide.



Prepared from 2,6-Dichloro-4-trifluoromethylbenzenesulfonyl chloride and 3-[2-(N,N-dimethylamino)ethoxy]-4-chloroaniline. MS (ES+) m/e 491 $[M+H]^+$

Example 6

N-[3-(2-Dimethylamino-ethoxy)-4-iodo-phenyl]-3,4-dimethoxy-benzenesulfonamide.



a). N-[3-(2-Dimethylamino-ethoxy)-4-iodo-phenyl]-acetamide

2-Iodo-5-acetamidophenol (2.15 g, 7.76 mmol) was dissolved in 1,2-dimethoxyethane (30 mL). 2-Dimethylaminoethyl chloride hydrochloride (1 eq, 7.76 mmol, 1.12 g) was added, followed by a solution of potassium carbonate (4 eq, 31.0 mmol, 4.30 g) in water (8 mL). The solution was heated to reflux, stirring at this temperature for 22 hours. The 1,2-dimethoxyethane was evaporated in vacuo and the residue was acidified to pH 1 using 3N hydrochloric acid. The mixture was washed 2 x ethyl acetate, and the aqueous portion basified to pH 11 using solid potassium carbonate. It was extracted 2 x ethyl acetate, dried over magnesium sulfate, filtered, and concentrated to afford the product (1.53 g, 57%) as a rust-colored oil.

MS (ES+) m/e 349 $[M+H]^+$

b). 3-(2-Dimethylamino-ethoxy)-4-iodo-phenylamine

To a solution of the compound of Example 1(a) (1.52 g, 4.39 mmol) in ethanol (22 mL) was added 10% aqueous sodium hydroxide solution (29 mL). The mixture was heated to reflux and allowed to stir at this temperature for 16 hours. It was cooled to room temperature and concentrated in vacuo. The residue was extracted 2 x ethyl acetate, dried over magnesium sulfate, filtered, and concentrated to furnish the product (1.13 g, 84%) as a rust-colored oil which solidified upon standing.

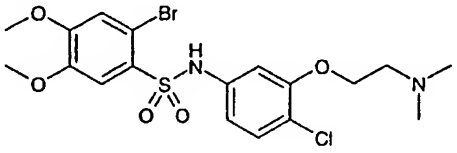
MS (ES+) m/e 307 $[M+H]^+$

c). N-[3-(2-Dimethylamino-ethoxy)-4-iodo-phenyl]-3,4-dimethoxy-benzenesulfonamide

To a solution of the compound of Example 1(b) (0.25 g, 0.81 mmol) in N,N-dimethylformamide (4 mL) was added 3,4-dimethoxybenzenesulfonyl chloride (1 eq, 0.81 mmol, 0.19 g). The pale orange solution was allowed to stir at room temperature for 23 hours. The crude product was purified via Gilson HPLC purification (10-90% acetonitrile/water over 5 minutes) and lyophilized overnight. The resulting hydochloride salt was azeotroped 1 x methanol and 1 x methylene chloride to furnish the product (0.16 g, 35%) as a fluffy white solid. MS (ES+) m/e 507 $(M+H)^+$

Example 7

2-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide



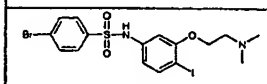
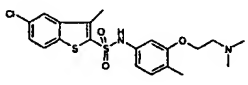
a). 2-Bromo-4,5-dimethoxy-benzenesulfonyl chloride.

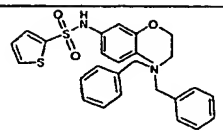
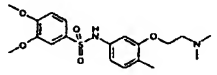
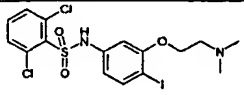
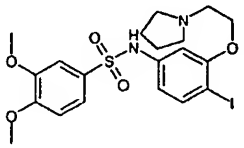
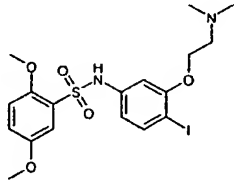
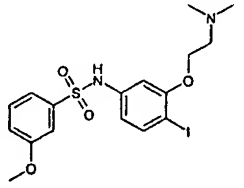
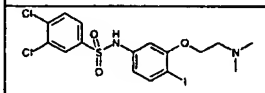
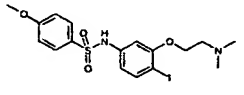
To a cooled (0 °C) solution of 4-bromoveratrole (15 mL, 100 mmol) in methylene chloride (100 mL) was added dropwise over 30 minutes chlorosulfonic acid (26 mL, 400 mmol). The resultant solution was allowed to warm to ambient temperature, maintained at this temperature for 3 hours, and then partitioned into a 1:1 methylene chloride/ice water mixture (500 mL). The organic layer was washed with water (2 x 200 mL) and brine (200 mL), dried (magnesium sulfate), and concentrated to give 2-bromo-4,5-dimethoxybenzenesulfonyl chloride (25 g, 78% yield) as a grey solid.

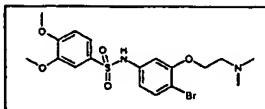
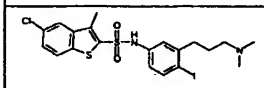
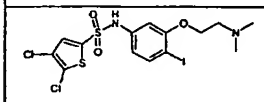
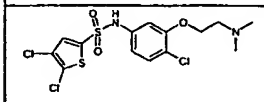
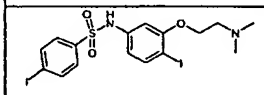
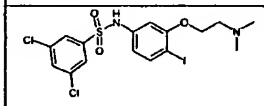
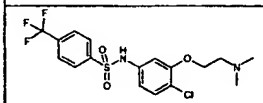
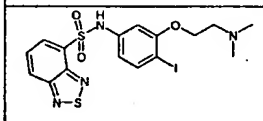
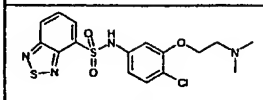
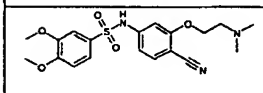
b). 2-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide.

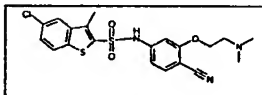
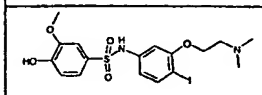
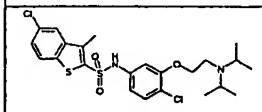
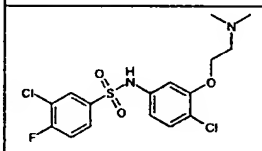
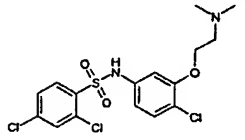
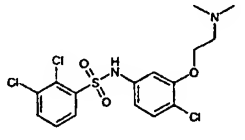
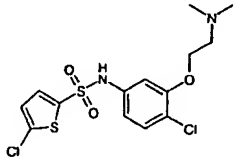
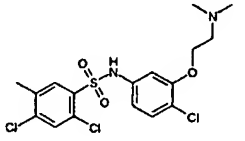
Prepared from 2-bromo-4,5-dimethoxy-benzenesulfonyl chloride and 3-[2-(N,N-dimethylamino)ethoxy]-4-chloroaniline using the general procedure of Example 1E above.

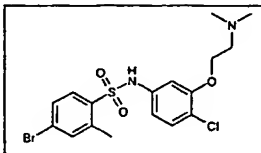
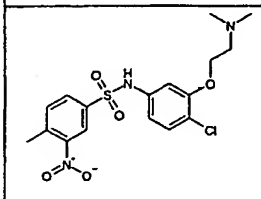
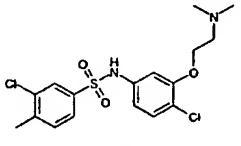
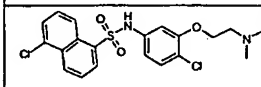
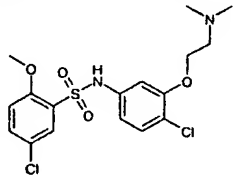
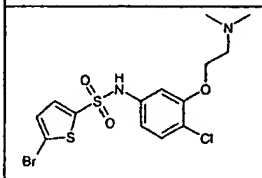
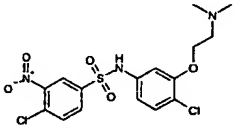
MS (ES+) m/e 494 $[M+H]^+$

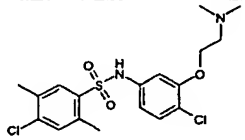
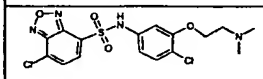
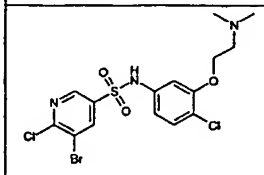
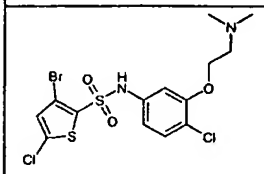
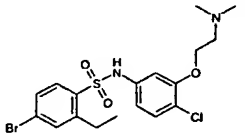
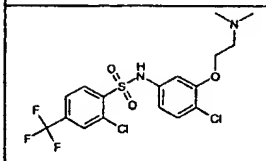
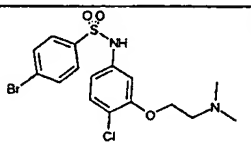
Example	Compound	MS (ES+) m/e [M+H]+
 8	4-Bromo-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	525
 9	5-Chloro-3-methyl-N-[4-methyl-3-(2-dimethylamino-ethoxy)-phenyl]-2-benzothiophenesulfonamide	439

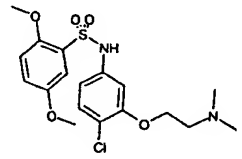
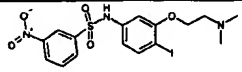
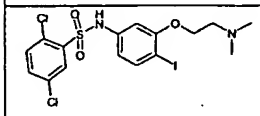
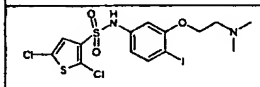
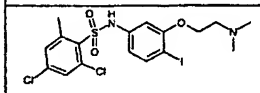
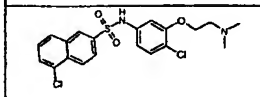
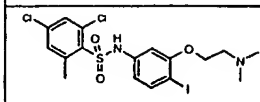
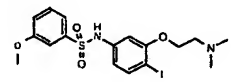
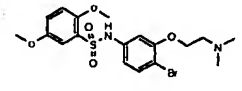
 10	N-[4-Methyl-3-(2-dibenzylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	493
 11	N-[4-Methyl-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide	395
 12	2,6-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	515
 13	N-[4-Iodo-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide	533
 14	N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-2,5-dimethoxy-benzenesulfonamide	507
 15	N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3-methoxy-benzenesulfonamide	477
 16	3,4-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	515
 17	N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-4-methoxy-benzenesulfonamide	477

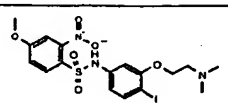
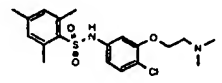
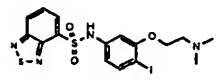
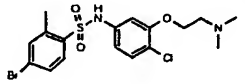
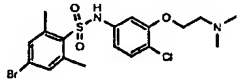
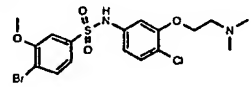
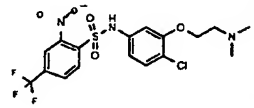
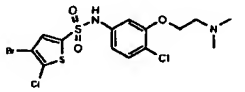
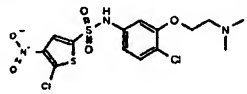
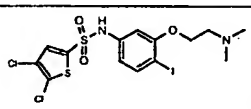
 18	N-[4-Bromo-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide	460
 19	5-Chloro-3-methyl-N-[4-iodo-3-(3-dimethylamino-propyl)-phenyl]-2-benzothiophenesulfonamide	549
 20	4,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	521
 21	4,5-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	429
 22	4-Iodo-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	573
 23	3,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	515
 24	4-Trifluoromethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	423
 25	N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzo-2,1,3-thiadiazole-4-sulfonamide	505
 26	N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzo-2,1,3-thiadiazole-4-sulfonamide	413
 27	N-[4-Cyano-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide	406

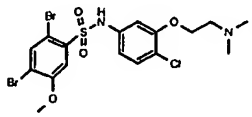
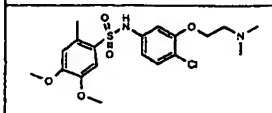
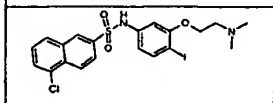
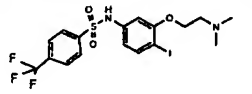
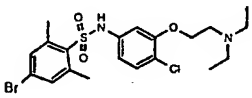
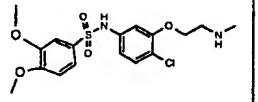
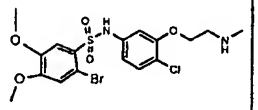
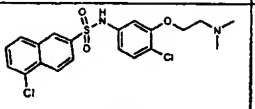
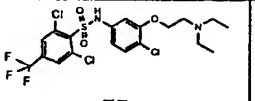
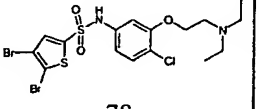
 28	5-Chloro-3-methyl-N-[4-cyano-3-(2-dimethylamino-ethoxy)-phenyl]-2-benzothiophenesulfonamide	450
 29	N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-4-hydroxy-3-methoxy-benzenesulfonamide	493
 30	5-Chloro-3-methyl-N-[4-chloro-3-(2-diisopropylamino-ethoxy)-phenyl]-2-benzothiophenesulfonamide	515/516
 31	3-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-fluoro-benzenesulfonamide	407
 32	2,4-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	423
 33	2,3-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	423
 34	5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	395
 35	2,4-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-5-methyl-benzenesulfonamide	437

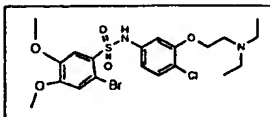
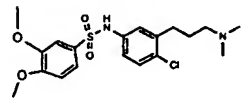
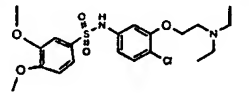
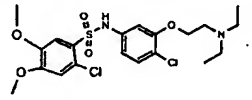
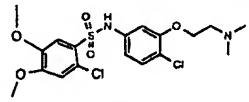
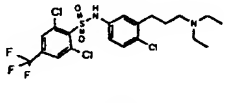
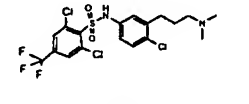
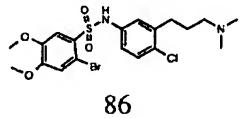
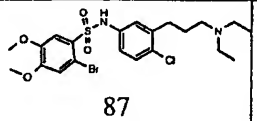
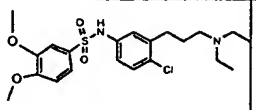
 36	4-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-methyl-benzenesulfonamide	447
 37	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-methyl-3-nitro-benzenesulfonamide	414
 38	3-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-methyl-benzenesulfonamide	403
 39	5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-1-naphthalenesulfonamide	439
 40	5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-methoxy-benzenesulfonamide	419
 41	5-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	439
 42	4-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3-nitro-benzenesulfonamide	434

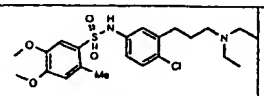
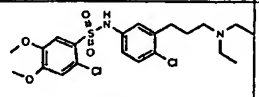
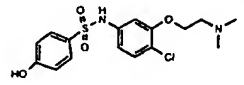
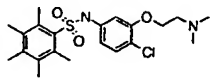
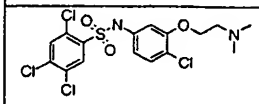
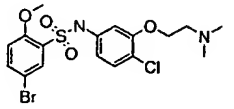
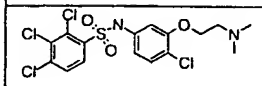
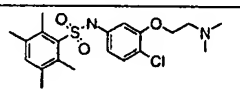
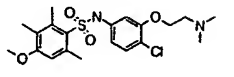
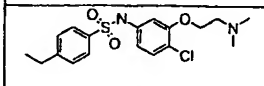
 43	4-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2,5-dimethyl-benzenesulfonamide	417
 44	N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzo[1,2,5]oxadiazole-4-sulfonamide	431
 45	5-Bromo-6-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3-pyridinesulfonamide	468
 46	3-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	473
 47	4-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-ethyl-benzenesulfonamide	461
 48	2-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide	457
 49	4-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	433

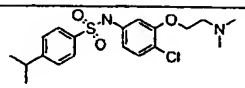
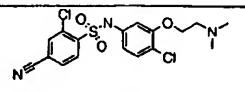
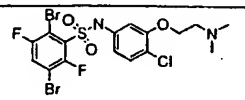
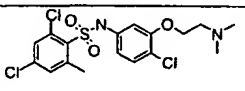
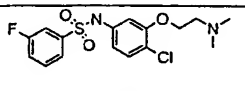
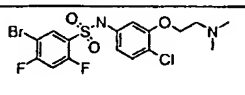
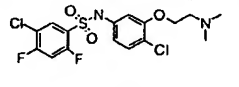
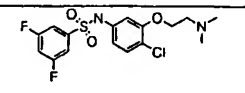
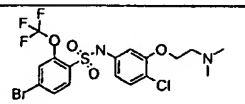
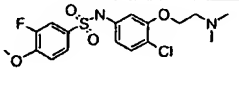
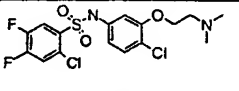
 50	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2,5-dimethoxy-benzenesulfonamide	415
 51	N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3-nitro-benzenesulfonamide	491
 52	2,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	514
 53	2,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3-thiophenesulfonamide	520
 54	2,4-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-6-methyl-benzenesulfonamide	528
 55	5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-naphthalenesulfonamide	439
 56	2,4-Dichloro-6-methyl-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	529
 57	3-Methoxy-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	477
 58	2,5-Dimethoxy-N-[4-bromo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	460

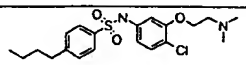
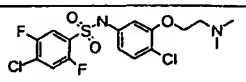
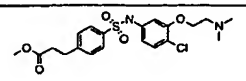
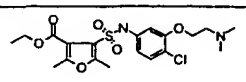
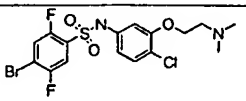
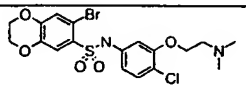
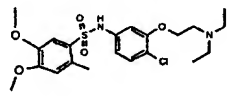
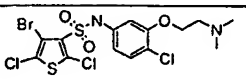
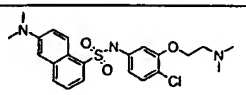
 59	2-Nitro-4-methoxy-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	522
 60	2,4,6-Trimethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	397
 61	N-[4-Iodo-3-(2-dimethylamino-ethoxy)phenyl]-benzo[1,2,5]-4-thiadiazolesulfonamide	505
 62	2-Methyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	447
 63	2,6-Dimethyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	462
 64	3-Methoxy-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	464
 65	2-Nitro-4-trifluoromethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	468
 66	4-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	474
 67	4-Nitro-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	440
 68	4,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	521

 69	2,4-Dibromo-5-methoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	543
 70	2-Methyl-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	429
 71	5-Chloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-2-naphthalenesulfonamide	531
 72	4-Trifluoromethyl-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	515
 73	2,6-Dimethyl-4-bromo-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide	490
 74	3,4-Dimethoxy-N-[4-chloro-3-(2-methylamino-ethoxy)-phenyl]-benzenesulfonamide	401
 75	2-Bromo-4,5-dimethoxy-N-[4-chloro-3-(2-methylamino-ethoxy)-phenyl]-benzenesulfonamide	480
 76	5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-naphthalenesulfonamide	439
 77	2,6-Dichloro-4-trifluoromethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide	519
 78	4,5-Dibromo-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide	547

 79	2-Bromo-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide	522
 80	3,4-Dimethoxy-N-[4-chloro-3-(3-dimethylamino-propyl)-phenyl]-benzenesulfonamide	413
 81	3,4-Dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide	443
 82	2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide	477
 83	2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	449
 84	2,6-Dichloro-N-[4-chloro-3-(3-diethylamino-propyl)-phenyl]-4-trifluoromethylbenzenesulfonamide	516
 85	2,6-Dichloro-N-[4-chloro-3-(3-dimethylamino-propyl)-phenyl]-4-trifluoromethylbenzenesulfonamide	488
 86	4,5-Dimethoxy-N-[4-chloro-3-(3-dimethylamino-propyl)-phenyl]-2-bromobenzenesulfonamide	491
 87	4.5-Dimethoxy-N-[4-chloro-3-(3-diethylamino-propyl)-phenyl]-2-bromobenzenesulfonamide	519
 88	3,4-Dimethoxy-N-[4-chloro-3-(3-diethylamino-propyl)-phenyl]benzenesulfonamide	440

 89	4,5-Dimethoxy-N-[4-chloro-3-(3-diethylamino-propyl)-phenyl]-2-methylbenzenesulfonamide	454
 90	4,5-Dimethoxy-N-[4-chloro-3-(3-diethylamino-propyl)-phenyl]-2-chlorobenzenesulfonamide	474
 91	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-hydroxybenzenesulfonamide	371
 92	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2,3,4,5,6-pentamethyl-benzenesulfonamide	425
 93	2,4,5-Trichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	457
 94	5-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-methoxy-benzenesulfonamide	463
 95	2,3,4-Trichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	457
 96	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2,3,5,6-tetramethyl-benzenesulfonamide	411
 97	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-methoxy-2,3,6-trimethyl-benzenesulfonamide	427
 98	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-ethyl-benzenesulfonamide	383

 99	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-isopropyl-benzenesulfonamide	397
 100	2-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-cyano-benzenesulfonamide	414
 101	2,5-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3,6-difluoro-benzenesulfonamide	547
 102	2,4-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-6-methyl-benzenesulfonamide	437
 103	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3-fluoro-benzenesulfonamide	373
 104	5-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2,4-difluoro-benzenesulfonamide	469
 105	5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2,4-difluoro-benzenesulfonamide	425
 106	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3,5-difluoro-benzenesulfonamide	391
 107	4-Bromo-N-[chloro-(2-dimethylamino-ethoxy)-phenyl]-2-trifluoromethoxy-benzenesulfonamide	517
 108	N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide	403
 109	2-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4,5-difluoro-benzenesulfonamide	425

 110	4-Butyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide	411
 111	4-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2,5-difluoro-benzenesulfonamide	425
 112	3-{4-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenylsulfamoyl]-phenyl}-propionic acid methyl ester	441
 113	4-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenylsulfamoyl]-2,5-dimethyl-furan-3-carboxylic acid ethyl ester	445
 114	4-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2,5-difluoro-benzenesulfonamide	469
 115	7-Bromo-2,3-dihydro-benzo[1,4]dioxine-6-sulfonic acid [4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-amide	491
 116	N-[4-Chloro-3-(2-diethylamino-ethoxy)-phenyl]-4,5-dimethoxy-2-methyl-benzenesulfonamide	457
 117	4-Bromo-2,5-dichloro-thiophene-3-sulfonic acid [4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-amide	507
 118	3-Dimethylamino-naphthalene-1-sulfonic acid [4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-amide	448

EXAMPLE 119

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Tablets/Ingredients	Per Tablet
1.Active ingredient (Cpd of Form. I)	40 mg
2.Corn Starch	20 mg
3.Alginic acid	20 mg
4.Sodium Alginate	20 mg
5.Mg stearate	1.3 mg
	2.3 mg

Procedure for tablets:

Step 1: Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2: Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3: The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4: The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5: The dry granules are lubricated with ingredient No. 5.

Step 6: The lubricated granules are compressed on a suitable tablet press.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

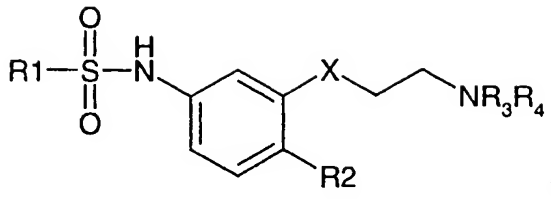
Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other

publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:



Formula (I)

wherein:

R_1 is phenyl, benzothiophenyl, thienyl, furyl, pyrrolyl, pyridinyl, benzthiadiazoyl, benzoxadiazoyl, quinolinyl, or naphthyl, all of which may be substituted or unsubstituted by one, two, three, four or five of the following: halogen, methoxy, OH, NO_2, YCF_3, C_{1-4} alkyl, $C_{(0-4)}alkylCO_2C_{(0-4)}alkyl$, cyano, $cycloC_{(1-4)}alkylenedioxy$, or dimethylamino;

R_2 is halogen, CN or methyl;

R_3 and R_4 are independently hydrogen, C_{1-6} alkyl or benzyl; or with the nitrogen form a pyrrolidine or piperidine ring;

X is O or CH_2;

Y is a bond or O;

provided the compound of Formula (I) is not 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [3-(2-dimethylamino-ethoxy)-4-iodo-phenyl]-amide;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 wherein R_1 is phenyl, thienyl, pyridinyl, benzthiadiazoyl, benzoxadiazoyl, or naphthyl, all of which may be substituted or unsubstituted by one, two, or three of the following: halogen, methoxy, NO_2, YCF_3, or C_{1-4} alkyl; R_2 is halogen; R_3 is alkyl; R_4 is alkyl; X is O, and Y is a bond.

3. A compound according to Claim 1 wherein R_1 is R_1 is phenyl, thienyl, pyridinyl, benzthiadiazoyl, benzoxadiazoyl, or naphthyl, all of which may be substituted or unsubstituted by one, two, or three of the following: halogen, methoxy, NO_2, YCF_3, or C_{1-4} alkyl; R_2 is halogen; R_3 is methyl or ethyl; R_4 is methyl or ethyl; X is O, and Y is a bond.

4. A compound according to claim 1 chosen from the group consisting of:

N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;

4-Bromo-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

N-[4-Methyl-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;

N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3-methoxy-benzenesulfonamide;

N-[4-Bromo-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;

N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;

4,5-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;

3,4-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,4,6-Trichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,6-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide;

2-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide;

4-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

4-Iodo-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,3-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3-Chloro-4-fluoro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3-Chloro-4-methyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,5-Dimethyl-4-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2-Chloro-4-trifluoromethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,4-Dichloro-6-methyl-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3-Methoxy-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,5-Dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,5-Dimethoxy-N-[4-bromo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3-Nitro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2-Nitro-4-methoxy-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3-Nitro-4-methyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2-Ethyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3,4-Dichlorophenyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,4,6-Trimethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

4-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-naphthalenesulfonamide;
5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
2,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3-thiophenesulfonamide;
5-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
4,5-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}methyl)-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzo[1,2,5]-4-thiadiazolesulfonamide;
2,4-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Methyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,6-Dimethyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Methoxy-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,4-Dichloro-5-methyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Nitro-4-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Nitro-4-trifluoromethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-1-naphthalenesulfonamide;
4-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
3-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
4-Nitro-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
4,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
7-Chloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzo[1,2,5]oxadiazole-4-sulfonamide;
5-Bromo-6-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3-pyridinesulfonamide;
2,4-Dibromo-5-methoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Methyl-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,6-Dimethyl-4-bromo-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3,4-Dimethoxy-N-[4-chloro-3-(2-methylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Bromo-4,5-dimethoxy-N-[4-chloro-3-(2-methylamino-ethoxy)-phenyl]-benzenesulfonamide;
5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-naphthalenesulfonamide;
2,6-Dichloro-4-trifluoromethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;
4,5-Dibromo-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
2-Bromo-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3,4-Dimethoxy-N-[4-chloro-3-(3-dimethylamino-propyl)-phenyl]-benzenesulfonamide;
3,4-Dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide; and
2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide.

5. A compund of Claim 1 chosen from the group consisting of:
N-[4-Chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;
4,5-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;
3,4-Dibromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,4,6-Trichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,6-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide;
N-[4-Iodo-3-(2-dimethylamino-ethoxy)-phenyl]-3,4-dimethoxy-benzenesulfonamide;
2-Bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide;
2,4-Dichloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2-Methyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
2,6-Dimethyl-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;
3-Methoxy-4-bromo-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,4-Dichloro-5-methyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3-Nitro-4-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2-Nitro-4-trifluoromethyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

4-Chlorophenyl-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

5-Chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-1-naphthalenesulfonamide;

4-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;

3-Bromo-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;

4-Nitro-5-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;

4,5-Dichloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;

7-Chloro-N-[4-iodo-3-(2-dimethylamino-ethoxy)-phenyl]-benzo[1,2,5]oxadiazole-4-sulfonamide;

5-Bromo-6-chloro-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-3-pyridinesulfonamide;

2,4-Dibromo-5-methoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2-Methyl-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2,6-Dichloro-4-trifluoromethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;

4,5-Dibromo-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-2-thiophenesulfonamide;

2-Bromo-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;

3,4-Dimethoxy-N-[4-chloro-3-(3-dimethylamino-propyl)-phenyl]-benzenesulfonamide;

3,4-Dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide;

2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-diethylamino-ethoxy)-phenyl]-benzenesulfonamide; and

2-Chloro-4,5-dimethoxy-N-[4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-benzenesulfonamide.

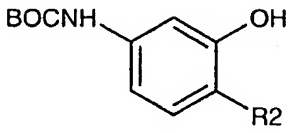
6. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

7. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

8. A method according to Claim 7 wherein the disease is congestive heart failure, stroke, ischemic heart disease, angina, myocardial ischemia, cardiac arrythmias, essential hypertension, pulmonary hypertension, COPD, restenosis, asthma, neurogenic inflammation metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function, or diabetes.

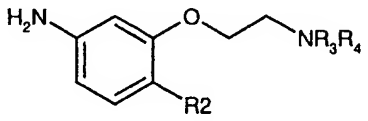
9. A process for preparing a compound of formula (I) of claim 1 by

a) alkylating a compound of formula (II):



II

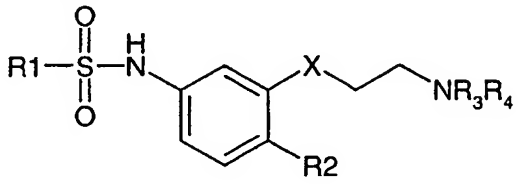
wherein R2 is halogen, CN or methyl;
with a dialkyl amino ethyl chloride;
b) deprotecting to provide a compound of formula (III):



III

wherein R3 and R4 are independently hydrogen, C_{1-6} alkyl or benzyl; or with the nitrogen form a pyrrolidine or piperidine ring; and

c) subsequent sulfonylation to provide a compound of formula (I):



I

wherein R1, R2, R3, and R4 are as defined in Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/34574

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/347, 361, 364, 443, 445, 452, 603, 604; 546/338; 548/126, 127; 549/51, 65, 366; 564/86, 87, 89, 92

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	US 5,795,892 A (VON DER SAAL et al.) 18 August 1998, see entire document.	1-6, 9 ----- 7, 8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 26 MARCH 2001	Date of mailing of the international search report 12 APR 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PETER G. O'SULLIVAN Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/34574

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K 31/18, 31/38, 31/335, 31/44, 31/425; C07C 303/38, 311/21, 311/29, 311/44; C07D 213/89, 271/12, 285/14, 333/34, 333/52, 333/72

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/347, 361, 364, 443, 445, 452, 603, 604; 546/338; 548/126, 127; 549/51, 65, 366; 564/86, 87, 89, 92